Review: Assessment and Management of Pain using WHO Ladder and Multimodal Approach

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ABSTRACT

The purpose of this review is to provide an approach to management of pain. Pain is frequently under recognized and inadequately treated. This review includes an overview of commonly use pain assessment and management modalities. A multifactorial way to deal with pain control is fundamental to upgrade periprocedural solace and limit the negative sequelae of uncontrolled pain in the patients.

Keywords: Pain Therapies, Pain Management, Pharmacological Approach, Non-Pharmacological Approach For Pain

INTRODUCTION

Pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage," but importantly, "inability to communicate verbally does not negate the possibility that an individual is experiencing pain and needs appropriate pain-relieving treatment." [1]

The English nervous specialist George Riddoch in an old-style paper from 1938 expressed about pain: "it is capable just irregularly in the existence of the sound, its neural mechanism lying lethargic, however cautious, fit to be stirred assuming the tissues of the body are undermined". Thusly, pain is an admonition about tissue harm announced explicit receptors and fiber frameworks reaching out from the periphery to the brain. At the point when the typical pathways are harmed, the quick outcome is misfortune or decrease of capacity including pain.[2]

The brain connection of pain starts at tangible receptors that send the aggravation sign to the dorsal horn of spinal line, then, at that point, up the spinothalamic plots to supraspinal focuses in brainstem, thalamus, and cerebral cortex. Tissues exposed to coordinate harmful boosts bringing about harm cause nociceptive pain, by which the difficult reaction is capable through pain receptors at the site of injury.[1]

Nociception is the physiology of genuine or potential tissue harm. Pain is the disagreeable considerations, feelings, and ways of behaving that go with nociception. There is wide variety in magnitude of experienced pain for a given nociception. Pain catastrophizing is an insufficient survival technique described by pointless groundwork for the most awful including rumination and vulnerability. More noteworthy disastrous reasoning is reliably connected with more noteworthy pain intensity. Expanded side effects of anxiety and depression and more prominent liquor use are additionally connected with higher pain force, though self-adequacy and less side effects of melancholy are related with less pain. Varieties in pain force and extent of restrictions are represented more by proportions of psychosocial parts of disease than by proportions of pathophysiology. There are likewise social contrasts in pain intensity and mitigation of pain with drug. Concentrates on archive great help with discomfort involving nonopioid medicine in patients recuperating from fracture surgery in The Netherlands and Vietnam. In the United States, in any case, patients who take more opioids in the clinic after fracture surgery have more pain and less fulfillment with lightening of pain. These discoveries propose that mental variables assume a huge part in the magnitude of the pain for a given nociception.[3]

Acute and chronic pain have been progressively perceived as being on a continuum, with their improvement impacted by the underlying pain experience and individual biopsychosocial factors. A study including grown-ups showed that during a three-month time span, 29% experienced low back pain, 17% encountered a headache or extreme migraine, 15% experienced neck pain, and 5% experienced facial or jaw pain. In a study of wandering office visits, analgesics were the most usually proceeded or recently endorsed drug at a pace of 11.4%.[4]

ROLE OF WHO LADDER IN PAIN ASSESMENT/ MANAGEMENT

In 1986, the World Health Organization (WHO) distributed a set of rules in regards to the utilization of analgesics in treating malignant growth pain and can likewise be utilized for patients with intense and constant nonmalignant pain. Adjuvant prescriptions can be started on a case-by-case basis at any progression of the ladder. It depicted a three-step approach of successive utilization of pharmacological specialists comparable with the pain level as revealed by the patient. This stepwise idea with functional proposals eponymously turned into the pain-relieving ladder which was subsequently converted into 22 dialects and became perhaps

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the most taken on guidelines for general pain treatment in the following multi decade.[5]

Aside from the decision of pharmacological specialists, the first pain relieving ladder expresses that:

- evaluation of the patient is essential before commencement and at regular intervals of therapy
- oral type of analgesics is favored at every possible opportunity
- pain relieving ought to be given at standard intervals as opposed to on request
- there is no normalized measurement and treatment ought to be individualized by the degree of pain as seen
- the focal point is to ease however much pain as could be expected
- adjuvant treatment ought to be added where important

Climbing from no treatment, the first ladder model beginnings with non-opioids (for example, anti-inflammatory medicine, paracetamol or nonsteroidal calming drugs, NSAIDs) for less than overwhelming pain, then expanding to feeble opioids like codeine and its subordinates as the second step for middle degree of pain, lastly heightening areas of strength for to like morphine, methadone and even fentanyl as the third step for the most elevated level of pain. [5] Patients with moderate or extreme pain got gentle opioids in 44.72% and 45.83%, separately, and among them, just 34.72% and 27.08% got strong opioids. The greater part of the patients denied opioids analgesics in light of worries in regards to the expected compulsion and unfavorable impacts

The significant lack in the ladder is that it truly does just accentuate the pharmacological treatment for pain, rather than sufficiently tending to that significance of nonpharmacological treatment and non-opioids treatment. The nonpharmacological and non-opioids treatments are the first-line restorative modalities suggested by the 2016 CDC Guideline for Prescribing Opioids for Chronic Pain. Our adaption of the analgesic ladder for CNCP (Chronic non-cancer pain) presented here depends on a similar standard. To start with, albeit integrative treatments are not displayed on the first Three-step pain relieving ladder graph, they can be considered at each progression of the changed ladder. The integrative clinical treatments including needle therapy, massage, yoga, unwinding, tai-chi, and spinal control for constant pain management, positive proof was found. Particularly impressive proof was noted for needle therapy as a correlative therapy for ongoing pain which could decrease the measurement of opioids analgesics or even possibly ease constant pain without dependence on opioids. Second, negligibly intrusive mediations ought to be considered in step 3 when the nonopioids and weak opioids have neglected to control the aggravation.[6] This update changes the step 3 to incorporate negligibly obtrusive interventional treatments, for example, nerve block, radiofrequency, spinal cord stimulation, spinal (epidural and subarachnoid) organization of local anesthetics, surgical intervention, and disc decompression, so on.

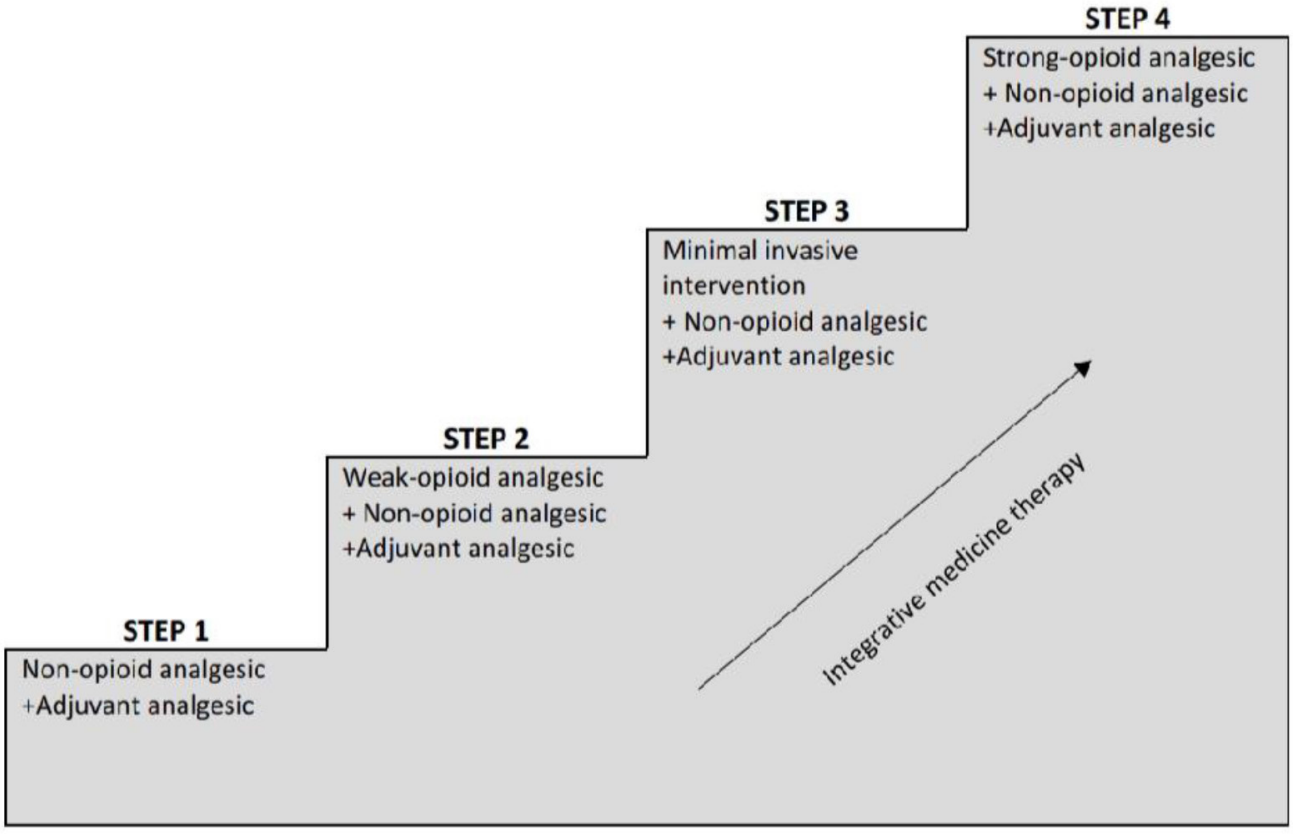

Figure-1: A generalized representation of a four-step analgesics ladder. Such four-step ladder, as opposed to the 1986 "ladder", reflects the advances in nonopioid modalities application for better pain relieving

MODE OF ACTION IN MANAGEMENT OF PAIN

Pain signals are carried by Aδ and C fibers of the primary neuron, which are activated through various noxious stimuli. Stimulation of nociceptors open voltage-gated sodium channels allowing sodium ions to pass into the cell causing depolarization which releases excitatory neurotransmitter from the nerve terminal like glutamate and substance P. these neurons synapse with secondary neuron in the substantia gelatinosa of the dorsal horn of spinal cord which have NMDA (N-methyl-D- aspartate) and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptors. Binding of neurotransmitters to NMDA and AMPA receptors leads to opening of VGNC (Voltage gated sodium channel) and VGCC (Voltage gated calcium channel) causing the release more action potentials. The neurons crossover to spinal cord and ascends to the thalamus as the spinothalamic tract. The two pathways to the brain through paleospinothalamic tract and neospinothalamic tract. These neurons synapse with tertiary neurons in the tertiary neurons in the thalamus and then reached to the somatosensory cortex. In this way, the brain perceives the pain.

In paleospinothalamic pathway some fibers terminate in the hypothalamus, periaqueductal gray matter of the midbrain and the reticular nuclei of the medulla. From midbrain, the signals reached down as an interneuron which synapse between the primary and secondary neuron at the spinal

Medication class	*Safety*	*Tolerability*	*Effectiveness**	*Price of generic (brand)†*	*Simplicity*
Acetaminophen	Hepatotoxicity Renal toxicity	Excellent	+	$0.04 ($0.18), 1,000 mg	325 to 650 mg orally every 4 to 6 hours *or* 1,000 mg orally 3 to 4 times daily Maximum: 4,000 mg per day
Aspirin	Bronchospasm GI irritation Platelet inhibition	Good: short-term Fair: long-term	++	$0.05 ($0.16), 650 mg	325 to 650 mg orally every 4 to 6 hours *or* 1,000 mg orally every 6 hours Maximum: 4,000 mg per day
Nonselective NSAIDs (e.g., ibuprofen)	GI irritation GI ulceration and bleeding Platelet inhibition Renal dysfunction Renal failure	Good	++	$0.21 ($0.60), 600 mg Cost varies by drug	200 to 400 mg orally every 4 to 6 hours Maximum: 1,200 mg per day (over-the-counter) 400 to 800 mg orally 3 to 4 times daily Maximum: 3,200 mg per day (prescription) Dosing varies by drug
Cyclooxygenase-2 selective NSAIDs (e.g., celecoxib [Celebrex])	Hepatic dysfunction Renal dysfunction	Good	++	NA ($5.72), 200 mg	100 to 200 mg orally twice daily
Opioid combinations (e.g., hydrocodone/acetaminophen)	Same as individual components	Good	+++	$0.20 ($1.83), 7.5 mg/500 mg Cost varies by drug	2.5 to 10 mg hydrocodone orally every 4 to 6 hours Maximum: 4,000 mg acetaminophen daily
Opioid (e.g., morphine)	Nausea/vomiting Respiratory depression Sedation	Good	+++	$0.25 (NA), 15 mg Cost varies by drug and formulation	10 to 30 mg orally every 3 to 4 hours Dosing varies by drug and formulation
Dual-action opioids (e.g., tapentadol [Nucynta])	Similar to opioids Serotonin syndrome (rare)	Good	+++	NA ($2.90), 50 mg	50 to 100 mg orally every 4 to 6 hours

FDA = U.S. Food and Drug Administration; GI = gastrointestinal; NA = not available; NSAID = nonsteroidal anti-inflammatory drug.

**—Based on information from Cochrane reviews regarding number needed to treat to produce 50% pain reduction at 4 to 6 hours (when available).[8-15]*

†—Estimated retail price per dose based on information obtained at http://www.goodrx.com (accessed March 6, 2013). Generic price listed first; brand price in parentheses.

Information from references 6 through 16.

Figure-2: Steps for Medications to Treat Acute Pain in Adults

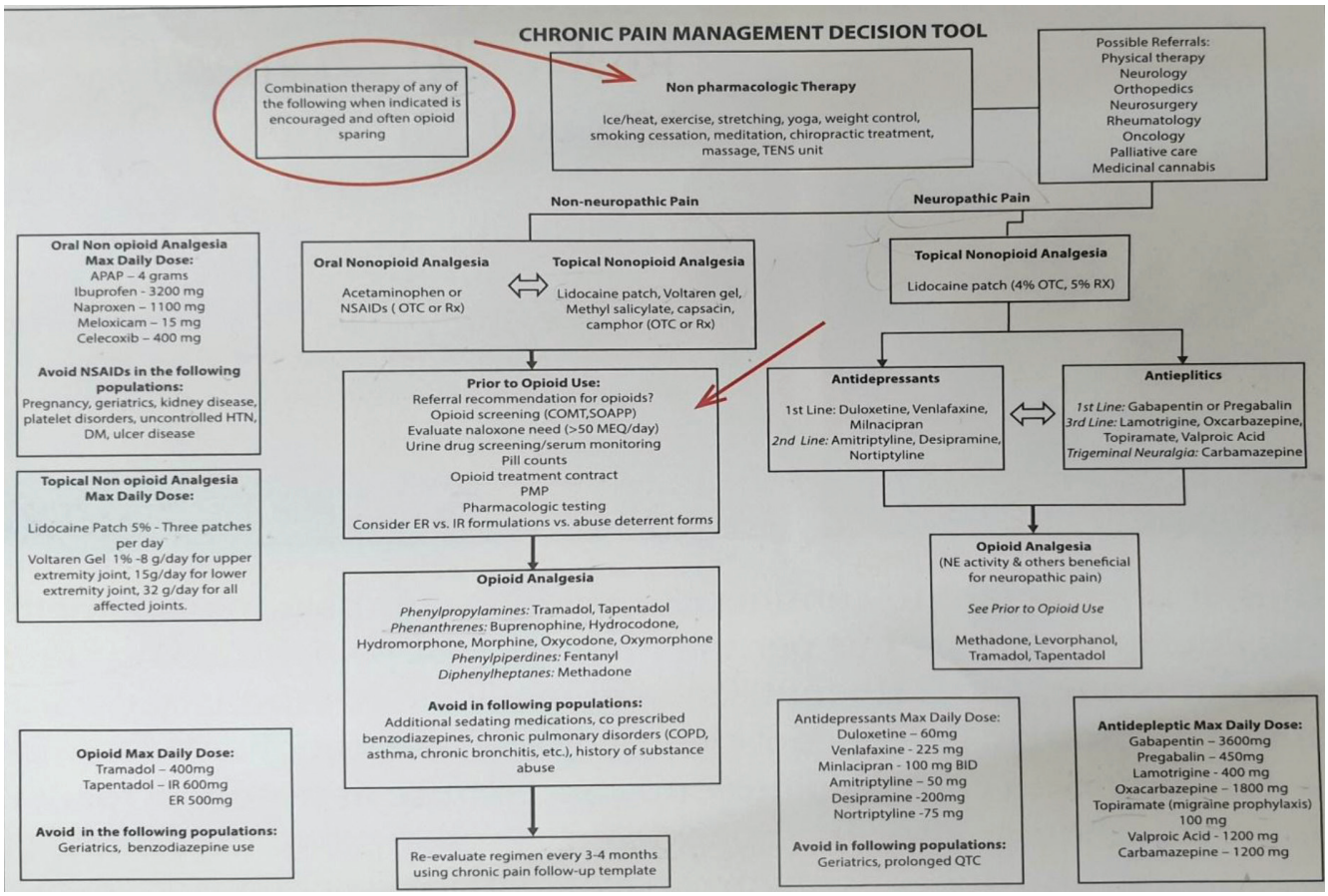

Figure-3: Multi Modal Approach for Clinical Decision of Chronic Pain Management

cord. The interneuron releases endogenous opioids such as enkephalin and inhibits the transmission of pain signals.

Enkephalin allows the opening of potassium channels causing the efflux of potassium ion which leads to intracellular hyperpolarization which in turn inhibits the action potential formation so less pain signals are transmitted to the brain and relieves pain. Enkephalin also inhibits NMDA receptor and VGCC channels which blocks the transmission of pain signals by blocking the binding of glutamate to NMDA and depolarization of calcium ion, respectively. Endogenous opioids play a major role in body's pain-relieving mechanism. There are some nuclei in brain stem called locus coeruleus in pons and locus raphae magnus in medulla releases Norepinephrine and serotonin respectively which are excitatory neurotransmitters, this activates the interneuron in the midbrain causing further release of enkephalin so, it inhibits the pain signal transmission.

Synthetic exogenous opioids perform same action as endogenous opioids, they act on the opioid's receptors especially in the spinal cord and also brain stem. Drugs that can bind to all three opioids receptors are full agonist for example morphine and those which bind selectively at specific receptors are partial agonists like buprenorphine.

Norepinephrine and serotonin promote endogenous opioids production so, antidepressants like SNRI, SSRI and TCA can relieve the pain by means of increasing excitatory neurotransmitters. Local and general anesthetics like lignocaine and ketamine respectively, reduce pain by blocking the VGSC channels and NMDA receptor respectively. Gabapentin reduces the pain by blocking the VGCC and it is effective for treating neuropathic pain.

Nociceptors are sensitized by pro-inflammation mediators such as prostaglandin, when tissue have damaged cell membrane phospholipid are converted to arachidonic acid, this activate the COX and LOX pathway from which the prostaglandin are produced. NSAIDS such as aspirin that inhibit COX pathway reduces the pain. Corticosteroids are also reducing the pain by blocking the conversion of phospholipid to arachidonic acid. These are the types of medication used to treat depends upon the severity of the pain.

ACUTE AND CHRONIC PAIN THERAPY

The way to deal with patients with acute pain starts by distinguishing the hidden reason and an illness explicit therapy. The first-line pharmacologic specialist for the indicative treatment of gentle to direct pain is acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID). The decision between these two prescriptions relies upon the kind of aggravation and patient risk factors for NSAID-related unfavorable impacts (for example, gastrointestinal, renovascular, or cardiovascular effects). Various NSAIDs make comparative pain- relieving impacts. Nonetheless, cyclooxygenase-2 selective NSAIDs (like, celecoxib) should be involved with alert in patients with cardiovascular risk factors and are more costly than nonselective NSAIDs.

On the off chance that these first-line specialists are not adequate for gentle to direct pain, prescriptions that target separate pathways at the same time, like an acetaminophen/ opioid's combination, are sensible decisions. Extreme acute pain is commonly treated with strong opioids. At each progression, adjuvant prescriptions coordinated at the underlying condition can be utilized. More up to date drugs with dual actions (for example, tapentadol) are likewise a choice. There is little proof that one opioid is predominant for pain control, yet there are a few pharmacologic contrasts among opioids. Due to the developing abuse and redirection of controlled substances, caution ought to be utilized while endorsing opioids, in any event, for momentary treatment. Patients ought to be educated to disposed the unused drugs appropriately.[4] The appraisal for basic circumstances, acute pain can be controlled utilizing transient pharmacologic therapy (with or without nonpharmacologic therapies). Customary assessment of pain control utilizing an aggravation scale permits the doctor to screen treatment adequacy and to decide when changes are justified. Booked, as opposed to depending on the situation dosing, gives more steady medication levels and consequently more predictable pain control.

Chronic pain is characterized as pain enduring past the standard course of recuperating or more than 3-6 months, which influences the singular's everyday working and prosperity. A few modifiable risk factors have additionally been distinguished including more pain catastrophizing, more noteworthy pain related dread, and more noteworthy side effects of anxiety, depression, and posttraumatic stress disorder. Distinguishing and tending to psychosocial elements might restrict tenacious pain.[3] It is a multifactorial issue, influencing generally 20% of the total populace. Persistent pain is answerable for more than 15% of patient visits and is related with critical interruptions in the personal satisfaction and profound prosperity. Persistent pain patients with coming about restricted movement are additionally bound to have comorbid conditions like depression, COPD, and diabetes. First-line therapy for some, constant pain conditions incorporate NSAIDs, antidepressants, anticonvulsants, and opioids. Notwithstanding, these treatment techniques are ineffective in a subset of patients. In the United States alone, as numerous as 34.7% of females and 26.7% of guys experience persistent pain. A study in India additionally viewed that as 63% of respondents announced their pain as serious instead of gentle or direct among patients with constant pain. [6-7]

MULTIMODAL APPROACH FOR CLINICAL DECISION OF PAIN MANAGEMENT

Multimodal analgesia includes the simultaneous utilization of essentially non-opioids analgesics to exploit the added substance, if not synergistic, impacts that produce superior analgesia while diminishing opioids use and opioids related side effects, also a critical part of multimodal pain the executives is the usage of local pain-relieving procedures, including peripheral and field blocks and neuraxial blocks (epidural absence of pain, for instance). The American Society of Anesthesiologists (ASA) team on acute pain the executives in 2012 suggested that multimodal pain management ought to be incorporated for the administration of perioperative pain whenever the situation allows.[8]

Following the solution opioids maltreatment emergency, the American Pain Society (APS) and the American Society of Anesthesiologists (ASA) have fostered a far-reaching proof-based rule for postoperative pain management. Of the various proposals, four were viewed as great proof and consequently emphatically suggested.

1. "… that clinicians offer multimodal analgesia, or the utilization of an assortment of pain-relieving prescriptions and methods joined with nonpharmacological intercessions, for the treatment of postoperative pain in children and adults"
2. "… that clinicians furnish adults and children with acetaminophen or potentially nonsteroidal anti-inflammatory drugs (NSAIDs) as a feature of multimodal analgesic for the management of postoperative pain in patients without contraindications"
3. "… that clinicians offer neuraxial analgesia for major thoracic and stomach methods, especially in patients at risk for heart complications, pneumonic inconveniences, or delayed ileus
4. "… that clinicians consider surgical site-explicit peripheral provincial sedative methods in adults and children for methodology with proof showing efficacy.[8]

ACETAMENOPHEN

Acetaminophen is a non-opioid, antipyretic pain relieving whose component of activity is as yet not totally perceived. It is profoundly specific and has an added substance and not really synergistic impact when combined with NSAIDs. The current guidelines prescribe to not surpass 3 g/day in a normal estimated adult to keep away from liver toxicity. Acetaminophen varies from different NSAIDs, as it needs significant anti-inflammatory action. Resent guidelines suggest its utilization as a planned portion instead of pro re nata (PRN; when necessary) and in combination with NSAIDs. It is for the most part very much endured, has not many medication drug interactions, isn't related with expanded blood pressure (likewise with NSAIDs), can be utilized during pregnancy (U.S. Food and Drug Administration [FDA] pregnancy class B), and is the pain relieving of decision for episodic use in patients with weakened renal capacity. Despite the fact that acetaminophen is less compelling for acute low back pain than certain NSAIDs, it is a sensible first-line choice in view of its great safety and cost profiles. [4,8]

NSAIDS

NSAIDs have been perceived to diminish opioids utilization by 25-30%, furnish predominant analgesia when combined with opioids, and have been proposed as first-line prescriptions for gentle to-direct pain. Nonselective NSAIDs repress both COX-1 and COX-2, though COX-2 specific NSAIDs have

more noteworthy COX-2 selectivity. Hindrance of COX-2 is remembered to intervene the pain-relieving properties of NSAIDs, while restraint of COX-1 gives off an impression of being related with gastrointestinal adverse effect. NSAIDs have anti-inflammatory impacts that are missing with acetaminophen, and they can be particularly helpful for the treatment of acute pain related with prostaglandin-mediated activity, like dysmenorrhea or osteoarthritis. Since most NSAIDs make almost indistinguishable analgesic effects, the decision depends on cost, dosing plan, and the recurrence or seriousness of adverse effects.

Effective NSAIDs are more compelling than placebo treatment for treating acute pain (e.g., from strains, sprains, contusions, or overuse injuries) in superficial areas, and the frequency of local and foundational adverse events is like placebo. Based on the number expected to treat, topical indomethacin isn't generally so successful as topical diclofenac (Solaraze), ibuprofen, ketoprofen, or piroxicam (not accessible in the United States), which are also effective. NSAIDs are avoid in pregnancy, geriatrics, uncontrolled HTN, ulcer disease. COX-2 selective NSAIDs are viewed as second-line prescriptions for gentle to direct pain since they have comparative adequacy to nonselective NSAIDs however with a more prominent cost. COX-2 specific NSAIDs and traditional NSAIDs are correspondingly successful for acute low back pain, yet COX-2 specific NSAIDs have less adverse effects. [4,6]

ADJUVANT ANALGESIC

Adjuvant analgesics characterized as " drugs that have primary indications other than pain but may be analgesic in selected circumstances ". It incorporates steroids, α-2-agonists like clonidine and dexmedetomidine, N-methyl-D-aspartate (NMDA) receptor antagonists, with ketamine as the essential model, yet additionally dextromethorphan, and magnesium controlled locally, intravenously (IV), or potentially as a part of local sedative combination, anti-spasmodic, Gabapentin, and intravenous Ketamine.

Central sensitization through the descending pathway includes a nociceptive sign that is potentiated in the peripheral sensory system, causing hyperexcitability in the spinal cord14 that is believed to be associated with actuating chronic as well as neuropathic pain. Subsequently, the dampening of central sensitization played a significant influence in the prevention and therapy of both postoperative pain and chronic pain. Ketamine, magnesium, methadone, and dexamethasone all have NMDA-blocking ability. [8,9]

OPIOIDS

Opioids might assist with giving successful relief from discomfort as a feature of a multimodal pain management plan. The impacts of opioids prescriptions are intervened through opioids receptors, situated in periaqueductal gray as well as all through the spinal cord, joint synovium and gastrointestinal mucosa. The analgesic impact is basically credited to the mu and kappa receptors.[10] Opioids, for example, hydrocodone and oxycodone are commonly combined with acetaminophen or a NSAID. In 2010, hydrocodone/acetaminophen was the most ordinarily administered medicine in United States. Prior to opioids use opioids screening (COMT, SOAPP), urine drug screening/ serum monitoring should be done.

Opioids combinations are more compelling than any one opioid for postoperative pain. Full opioids agonists, like morphine, are powerful analgesics that might be utilized if opioids combined with acetaminophen or NSAIDs are deficient to control moderate to extreme pain. Adverse effect of opioids incorporates nausea, vomiting, constipation, sedation, pruritus, urinary maintenance, and respiratory depression. It has comparative viability as oxycodone for intense pain, with a fundamentally lower frequency of nausea, vomiting, constipation.[11] Opioids are avoided in the population additional sedating medications, chronic bronchitis, co-prescribed benzodiazepines and history of substance of abuse.

NON-PHARMACOLOGIC TREATMENT OPTION

The multimodal way to deal with pain management likewise incorporates non-pharmacologic choices. These incorporate the two physical and psychological strategies. Patients might profit from massages, heat packs, ice packs, repositioning, or some active work (like walking or sitting up in a seat for a brief timeframe). A few patients might track down cognitive behavioral strategies, like utilizing symbolism or relaxation, yoga, chiropractic treatment to be useful. In pediatric patients, hypnosis has been demonstrated to be viable for lessening pain.[12] It has been laid out that anxiety, catastrophizing, and depression can influence how a patient encounters pain and can irritate or prolong acute pain. The Joint Commission21 American School of Doctors (ACP) Public Thorough Malignant Growth Organization (NCCN)24 and American Culture of Clinical Oncology (ASCO)11 rules all suggest a blend of pharmacologic and nonpharmacologic modalities. [13] non-pharmacologic mediations are a significant piece of an extensive aggravation management plan. They incorporate procedural and psychosocial intercessions. Procedural intercessions, for example, radiation to bone metastasis, nerve square, and neurectomy, are effective however generally saved for serious pain unmanageable to drugs. Psychosocial intercessions, like cognitive behavioral therapy, relaxation, and experiential interventions, yoga is related with less incidental effects and ought to be important for a multimodal way to deal with pain the management.[12]

CONCLUSION

In this review article, we attempt to provide and describes the pain and its management using the WHO Ladder and a true multimodal approach for chronic and acute pain and offer the additional treatment options for patients. Pain is an admonition about tissue harm announced explicit receptors and fiber systems extending from the periphery to the brain. Modified/revised WHO ladder open a path for more effective pain management as it includes interventional therapies in step 3 if weak opioids and adjuvant analgesics fail,

interventional therapies may be considered before moving on to strong opioids. The clinical approach for decision of pain management includes patient's specific risks and selection of the specific drug with their individualization; that is non-opioids before opioids, prior to opioids use opioids screening (COMT, SOAPP), opioids that control both peripheral and central sensitization. Patient safety and improving their quality of life by approaching to the different strategies which includes cognitive non pharmaceutical and pharmaceutical strategies. This review will provide guidance for primary health care clinicians in both acute and chronic pain management.

DISCLOSURE

The author reports no conflicts of interest in this work.

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